#52

The opinion in support of the decision being entered today is not binding precedent of the Board.

Paper 263

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

ROBERT C. **ROSE**,
WILLIAM BONNEZ and RICHARD C. REICHMAN,

Junior Party,
(Application 08/207,309)

v.

IAN **FRAZER** and JIAN ZHOU,

Senior Party.
(Application 08/185,928)

Patent Interference 104,773

DOUGLAS R. **LOWY**,
JOHN T. SCHILLER and REINHARD KIRNBAUER,

Junior Party,
(Application 08/484,181)

v.

IAN **FRAZER** and JIAN ZHOU,

Senior Party.
(Application 08/185,928)

Patent Interference 104,775

IAN **FRAZER** and JIAN ZHOU,

Junior Party
(Application 08/185,928)

v.

C. RICHARD **SCHLEGEL** and A. BENNETT JENSON,

Senior Party
(Application 08/216,506).

Patent Interference 104,776

Before: McKELVEY, Senior Administrative Patent Judge, LANE, TIERNEY, MOORE, and NAGUMO, Administrative Patent Judges.

NAGUMO, Administrative Patent Judge.

DECISION – FRAZER PRIORITY DATE – BD.R. 125(a)

Initial Observations

The subject matter involved in six related, but separate, Interferences 104,771 through 104,776 involves complicated biotechnology. At the outset of each interferences, the parties were advised that it would be helpful if presentations could be made using "plain English" (Paper 3). Instead, counsel for the parties have all elected to present their respective cases (both testimony and briefs) in large measure using "biotechese". We have not been able to find that any attempt was made by the parties to present a useful glossary of terms referenced directly in the briefs. We have also not been able to find any attempt to

have a witness explain the technology in more basic terms. We have not been able to find in a brief a "plain English" explanation of the subject matter involved. In short, there was no attempt to educate the board in simple terms on the technology involved. We do not know why the parties basically chose to ignore Paper 3.

If the kind of exposition we are asking for were easy to write, we probably would not need to ask parties to read and comply with ¶ 43 ("Reliance on scientific tests and data") of the Standing Order (Paper 2). The study and practical applications of complex subjects leads, necessarily, to sophisticated, technical concepts, which tend to be expressed in sophisticated, technical language. Concepts that have been reduced to things that are "patentable subject matter," however, can usually be explained to an audience in terms that explain the concepts while avoiding the technical jargon. Such explanations are not "dumbing down" the subject matter. The lack of a plain English technical background has made the case difficult to decide. Examples follow.

Rose

The Rose claims require that L1 protein in virus-like particles be recognized by sera obtained from (human) patients exposed to certain viruses. What, exactly,

are "sera"? What is in them as a result of exposure to a virus and what else might be present? What tests are done to see if the L1 protein is "recognized"? What does the recognition imply about the shape of the L1 protein, and why?

Lowy

The Lowy claims call for capsids or virus-like particles capable of inducing high-titer neutralizing antibodies. What is a neutralizing antibody? How are titers measured in the laboratory, and when is a titer a "high titer"? How does one determine that an antibody is neutralizing?

Schlegel

The Schlegel claims call for L1 protein that "exhibits the same conformation" as the L1 protein on the surface of an intact human papillomvirus. Many of its proofs involve a certain kind of "ELISA" measurement. What is actually measured? What is the significance of what is measured?

Frazer

> Frazer, due to the nature of its case, does not offer proofs for priority based on laboratory notebooks or the outcome of particular experiments. But its case requires that we understand the descriptions in its specifications and printed publications of the results of recombinant DNA technology, the production of proteins, and the assembly of proteins into particles resembling viruses.

A number of questions arose as we considered the laboratory experiments, measurements, and technical arguments on which the parties relied to prove conception or actual reduction to practice. How was the experiment done? What was actually measured? How reliable is the measurement? What controls ought to be done? Why? What is the level of the signal compared to the noise? How reproducible is the assay? How do the measurements relate to the conclusions the moving party would have us draw from its experiments? Why is the movant's proposed explanation the most likely explanation? What else could have led to the same result? These are the types of questions that ¶ 43 of the Standing Order indicates should be explained. We often found ourselves asking these questions as we sought to

resolve the issue of priority in this interference. Seldom, however, could we find a simple, straightforward explanation in the briefing or in the record. Perhaps the parties assumed--erroneously--that we knew all about the experiments. What is absolutely plain is that all parties simply did not comply with the provisions of ¶ 43 of the Standing Order (Paper 2, page 30).

As a result, we have spent a good amount of time searching the record for the teachings we requested in ¶ 43 of the Standing Order. We have spent additional time assuring ourselves that our understanding, expressed in plain English, is accurate. We have attempted to summarize the major features of the involved technology for the general reader in Appendix I, which is attached to this decision. We remain somewhat nonplused that the parties would provide so little guidance to the technical foundations of their cases.

As indicated during oral argument during the priority phase, we had hoped to have final decisions entered in these six interference on or before 15 August 2005. Instead, final decisions are being entered about a month later. The "delay" in entering final decisions in large measure can be attributed to the lack of a "technical education" in "plain English" by each of the parties.

In future cases, our hope is that parties take the time to educate the board in "plain English" on the nature of the technology involved in an interference.

I. Introduction

This is a decision on Frazer's priority date. Oral arguments in related interferences 104,771 through 104,776 were held on 30 June 2005 before a court reporter. (Transcript of hearing, Paper 261.) Michael Goldman, Esq., argued for Rose. Brent Babcock, Esq., and Nancy Vensko, Esq., argued for Lowy. Beth Burrous, Esq., argued for Frazer. Elliot Olstein, Esq., argued for Schlegel.

For the reasons set out *infra*, we hold that Frazer has not proven a date of conception, actual reduction to practice, or constructive reduction to practice prior to the filing date of its PCT application. Moreover, we find that even if Frazer had proved conception, it has not proved reasonable diligence by activities in the United States from any of its proposed dates of conception through a reduction to practice. Thus, the earliest date of invention to which Frazer is entitled is 20 July 1992, the date for which Frazer has been accorded the benefit for priority.

Contents

Frazer's priority case against Rose (104,773)

In interference 104,773, Frazer, as the senior party, needs to prove its priority case against Rose only if Rose rebuts the presumption that Frazer is the prior inventor. Rose do this by, for example, establishing prior conception followed by reasonable diligence until a reduction to practice from a time prior to Frazer's constructive reduction to practice on 20 July 1992. As explained in the opinion for the Board authored by Administrative Patent Judge Lane, Rose failed to provide adequate corroboration of Rose's conception, and therefor it failed to prove conception prior to Frazer's constructive reduction to practice. Accordingly, we need not consider Frazer's priority case against Rose in interference 104,773. We note, however, that Frazer's case for priority based on dates earlier than its accorded benefit date, as against Rose, is substantially the same as Frazer's priority case against Schlegel. The principal difference is that against Rose, Frazer also relies on its alleged conception of claims 89 and 91, which provide alternative definitions of the Count in interference 104,773.

Frazer's priority case against Lowy (104,775)

In interference 104,775, Frazer, as the senior party, needs to prove its priority case against Lowy only if Lowy rebuts the presumption that Frazer is the prior inventor. As explained in

the opinion for the Board authored by Administrative Patent Judge Moore, Lowy failed to prove conception or an actual reduction to practice prior to Frazer's constructive reduction to practice. Accordingly, we need not consider Frazer's priority case against Lowy. We note, however, that Frazer's case for priority based on dates earlier than its accorded benefit date, as against Lowy, is substantially the same as Frazer's priority case against Schlegel. The principal difference is that against Lowy, Frazer also relies on its alleged conception of claim 89, which provides an alternative definition of the Count in interference 104,775.

Frazer's priority case against Schlegel (104,776)

In interference 104,776, Frazer, as the junior party, bears the burden of proving, by a preponderance of the evidence, that it was the prior inventor of the subject matter of Count 2, the sole count in the interference. Frazer submits two major arguments. First, Frazer argues Schlegel derived the invention from Frazer – more specifically, that Frazer conceived the invention prior to Schlegel, and that Frazer then communicated the invention to Schlegel inventors, Dr. Schlegel and Dr. Jensen, at a Papillomavirus Workshop in Seattle, Washington, in July 1991. In the alternative, Frazer argues that Schlegel does not have a constructive reduction to practice of Count 2. In effect, Frazer argues that the Board erred in according Schlegel

the benefit for priority of its original application and its involved continuation application with respect to Count 2.

In the following discussion of Frazer's priority case, we concentrate on its arguments as against Schlegel in interference 104,776, because that is the only interference in which Frazer bears the burden of proof. In interferences 104,773 and 104,775, Frazer's opponents, Rose and Lowy, respectively, failed to carry their burden to establish a prima facie case that they were the first to invent, within the meaning of 35 U.S.C. §§ 102(g) and 135(a). Accordingly, we need not and shall not consider Frazer's additional arguments for earlier dates of conception and actual or constructive reductions to practice in those interferences.

II. Findings of fact

The following findings of fact, and those set out in the discussion, are supported by a preponderance of evidence in the record.[1]

[1] To the extent these findings of fact discuss legal issues, they may be treated as conclusions of law.

The parties

Frazer

1. Frazer's involved 08/185,928 (928) application was filed 19 January 1994, as the national stage (35 U.S.C. § 371) of: PCT Application PCT/AU92/00364 (PCT), filed 20 July 1992, and

Australian application PK 7322 (Australian), filed 19 July 1991.

The 928 application is entitled "Papillomavirus vaccines".

2. Frazer has been accorded the benefit for priority of the PCT application.

3. The PCT application contains significantly more disclosure than the Australian application.

4. As a result of the Decision on Preliminary Motions, Frazer has been denied the benefit for priority of the Australian application.

5. The named inventors of the 928 application are Ian Frazer and Jian Zhou (deceased, 1999).

6. Frazer's real parties-in-interest are CSL Limited (Australia) and University of Queensland (Australia). Merck & Co., Inc., is a licensee.

Schlegel

7. Schlegel's involved application, 08/216,506 (506) was filed 22 March 1994.

8. The 506 application was filed as a continuation of the 07/903,109 (109) application, which was filed 25 June 1992.

9. Schlegel has been accorded the benefit for priority of the 109 application.

10. Schlegel's involved application is entitled "Human papillomavirus vaccines containing conformationally correct L1 capsid proteins."

11. The named inventors of the 506 application are C. Richard Schlegel and A. Bennett Jenson.

12. The Georgetown University School of Medicine is Schlegel's real party-in-interest. MedImmune, Inc. and SmithKline Beecham PLC are licensees.

The Count (104,776)

As a result of the Decision on Preliminary Motions (Paper 175), the interference 104,776 was redeclared with the following Count (Paper 178):[2]

[2] The Decision on Rehearing (Paper 194) did not alter the Count.

Count 2

A composition of matter according to claim 67 of Frazer or a method according to either of claims 65 or 97 of Frazer.

(Paper 176 at 2.)

The allowable claims of the parties are:

Frazer 65-80, 97-100

Schlegel 14, 16, 23-25.

The claims that correspond to the Count are:

Frazer 65-80, 97-100

Schlegel 14, 16, 23-25.

The claims that do not correspond to the Count and therefore are not involved in this interference are:

Frazer none

Schlegel none.

(Paper 178 at 3.)

13. Frazer claim 67 reads:

A papillomavirus virus-like particle made by the method of claim 65.

14. Frazer claim 65 reads:

A method of making a papillomavirus virus-like particle, which method comprises: constructing a recombinant DNA molecule that contains a sequence encoding a papillomavirus L1 protein; transfecting a host cell with the recombinant DNA molecule; expressing papillomavirus L1 protein in the host cell; and obtaining papillomavirus virus-like

particles from the transfected host cell; wherein the papillomavirus is not HPV 16.

15. Frazer claim 67, expanded to include the limitations of Frazer claim 65, reads:

> A papillomavirus virus-like particle made by the method comprising: constructing a recombinant DNA molecule that contains a sequence encoding a papillomavirus L1 protein; transfecting a host cell with the recombinant DNA molecule; expressing papillomavirus L1 protein in the host cell; and obtaining papillomavirus virus-like particles from the transfected host cell; wherein the papillomavirus is not HPV 16.

16. Frazer claim 97 reads:

> A method of producing anti-papillomavirus antibodies in an animal comprising administration of a papillomavirus virus-like particle to the animal.

Procedural background

At the declaration of these interferences, Frazer was the senior party. In interference 104,776, a motions panel, as explained in the Decision on Preliminary Motions (Paper 175), determined that none of the Schlegel claims that defined alternatives of Count 1 was patentable to Schlegel. Moreover, Frazer claims 89 and 91, which defined alternatives of Count 1, were found to lack an adequate written description. (*Id.*) Frazer was also denied benefit for priority of its Australian application. (*Id.*) The interference was redeclared with

Count 2. (Paper 176.) Frazer, having been denied the benefit for priority of its Australian application (FX 1050), was designated the junior party. (Paper 176 at 2.) Frazer timely requested reconsideration of the Board's decision denying Frazer the benefit of its Australian application. (Paper 181 at 1.) Frazer urged that reconsideration in its favor would result in redeclaration of the interference with Frazer as senior party. (Paper 181 at 1 and at 16.) Frazer also urged that Frazer preliminary motion 4, seeking judgment that Schlegel's claims lacked an enabling disclosure, should be granted. (Paper 181 at 1 and at 13-15.) The original motions panel denied these requests for reconsideration. (Paper 194.)

Frazer also requested reconsideration at final hearing of the Board's denial of Frazer preliminary motions 2 and 3, seeking judgment that certain Schlegel claims were unpatentable over prior art. (Paper 198.) These requests were denied by the panel that heard the preliminary motions. (Paper 256.)

Schlegel also timely sought reconsideration of the Board's Decision, in particular, the Board's grant-in-part of Frazer preliminary motion 2, that certain Schlegel claims were unpatentable over U.S. patent 5,071,757 to Kreider (FX 1007), and the denial of Schlegel preliminary motion 8, to add claims to Schlegel's application, as well as the consequent dismissal of

its preliminary motions contingent on the grant of Schlegel preliminary motion 8. (Paper 182.) The original motions panel denied these requests for relief. (Paper 194.)

Schlegel requested review at final hearing of the decision on Schlegel preliminary motion 8 and the contingent motions, and further requested reconsideration of the redeclaration with Count 2. (Paper 203.) These requests were dismissed as an improper second request for reconsideration and as an untimely responsive motion to change the Count, respectively. (Paper 256.)

Summary: technical background of Frazer's priority case

A general description of the technical background to the issues in this interference is provided in the Appendix to this opinion.

Each of Frazer's claims that are present as alternative definitions of the Count in this interference recites the presence of virus-like particles made from the L1 capsid protein of a papillomavirus. Claims 65 and 67 exclude human papillomavirus 16 ("HPV-16") as the papillomavirus that can provide the capsid proteins. Claim 97 covers methods of producing antibodies to papillomaviruses by administering virus-like particles to an animal. The motions panel held that, in order to be useful within the meaning of 35 U.S.C. § 101, virus-

like particles must have conformational epitopes of the native virions.

The HPV-16 particles disclosed by Frazer in the Austalian and PCT applications were significantly smaller (average diameter reported to be 35-40 nm) than all known papillomaviruses (diameters reported to be 50-60 nm). Moreover, there was no immunological evidence indicating the presence of conformational epitopes. On this basis, the motions panel found sufficient evidence to doubt the objective truth of the proposition that Frazer's HPV-16 virus-like particles had such conformational epitopes. Our findings were strengthened by the discovery reported in two papers by the Lowy inventors and coworkers that the prototype HPV-16 L1 DNA had a critical single base-pair mutation compared to HPV-16 DNA obtained from a less advanced cervical lesion that resulted in L1 protein having a different amino acid at a single location. That single difference proved to be critical. Lowy found that the recombinantly expressed "wild type" HPV-16 L1 formed numerous virus-like particles that reacted with antibodies to the virus, whereas the prototype HPV-16 L1 produced relatively few virus-like particles, which did not react with antibodies to the HPV-16 viruses.

As discussed in more detail infra, the picture is more complicated following Frazer's assertion that it has, following

the decision on preliminary motions, shown that it actually used a "wild type" L1 gene. Frazer has not, however, come forward with evidence that the particles it made had wild type conformational epitopes, not withstanding the small size and irregular shapes of the particles. Frazer also admits that it (along with the rest of the relevant research community) thought that it had used the prototype HDV16 L1 DNA.

As discussed extensively in the decisions on preliminary motions (104,773, Paper 197; 104,775, Paper 149; 104,776, Paper 175), Frazer maintains that the formation of virus-like particles is sufficient evidence to conclude that the coat proteins had the molecular conformation – and hence the same conformational epitopes – of the native virion. Frazer's opponents deny that the presence of virus-like particles is dispositive and insist that immunological testing is necessary to establish the existence of conformational epitopes. The motions panel determined that the preponderance of the evidence was against Frazer.

For the foregoing reasons, the motions panel declined to accord Frazer the benefit for priority of its Australian application, which disclosed only particles containing both L1 and L2 HPV-16 prototype protein, but which did not disclose that the particles had virion conformational epitopes. As for

Frazer's PCT application, the motions panel held that none of the opposing parties had carried their burden of establishing a substantial reason to doubt that the normal appearing virus-like particles reportedly made from L1 protein of other papillomaviruses (HPV-6, HPV-11, and bovine papillomavirus-1 ("BPV-1"), none of which are described in the Australian application) had conformational epitopes of the natives viruses. Accordingly, the benefit for priority accorded to Frazer on the basis of its PCT application was not disturbed.

Frazer's priority case

17. Frazer asserts that it has proved conception of alternative embodiments of Count 2 within the scope of Frazer claims 65, 67, and 97. (Paper 198 at 6.)

18. According to Frazer, a Zhou abstract (FX 1358), the manuscript (FX 1249) that was subsequently published as *Zhou 1991* (FX 1001), and Dr. Frazer's and Dr. Zhou's disclosures at the Seattle Papillomavirus Workshop in July 1991 were all complete and enabling disclosures of embodiments of the Count. (Paper 198 at 27-33.)

19. Frazer urges that Schlegel derived the invention from Frazer. (Frazer Principal Brief, Paper 198 at 2.)

20. Frazer argues that it conceived the invention prior to Schlegel and communicated a complete and enabling conception of

the Count to each of the Schlegel inventors, Dr. C. Richard Schlegel and Dr. A. Bennett Jenson, at a July 1991, Papillomavirus Workshop in Seattle, Washington, prior to Schlegel's conception. (Paper 198 at 2-3 and 4-26.)

21. Frazer relies on the work reported in its Australian application relating to particles derived from a clone of HPV-16 as evidence of conception.

22. Frazer offers new evidence, developed after the Decision on Preliminary Motions (Paper 175) that, in its view, shows that "the HPV16 working examples in the Frazer provisional and PCT applications were conducted with wild type HPV16, not prototype." (Paper 198 at 3.)

23. Accordingly, Frazer argues that "any negative data pertaining to prototype HPV16 is irrelevant to Frazer's reduction to practice." (Paper 198 at 3.)

24. Frazer urges that the evidence before the Board shows that the Australian application describes and enables the subject matter of the Count, as required for a constructive reduction to practice. (Paper 198 at 3.)

25. Frazer does not allege that there is any experimental evidence demonstrating that the HPV-16 virus-like particles disclosed in its Australian application have conformational epitopes of the native HPV-16 viruses, or that they are

recognized specifically by antibodies that recognize conformational epitopes on the native HPV-16 virus.

26. Frazer acknowledges that all of the laboratory work on which Frazer relies for conception and actual reduction to practice occurred outside of the United States, in Australia. (Frazer deposition, FX 1466 at 287-290.)

27. A motions panel of the Board held that Frazer was not entitled to the benefit for priority of Frazer's Australian application, PK 7322 (FX 1050). (Paper 175 at 45-68 and 128.)

28. Frazer urges that certain activities in Australia, particularly Dr. Frazer's correspondence of 11 June 1991, to Dr. Brandon (FX 1232), are admissible on the issue of derivation. (Paper 198 at 6.)

29. Dr. Frazer's correspondence of 11 June 1991, includes a cover letter and a manuscript of the *Zhou 1991* publication. (FX 1232.)

30. The cover letter includes the instruction that "it is most important that the general concept of using recombinant L1 and L2 proteins of papillomavirus of any genotype to produce virions which self-assemble to make and immunogenic papillomavirus be included in the patent." (FX 1232 at 1.)

31. In the event that the Board does not accept Frazer's Australian application as evidence of conception in spite of the

new evidence regarding the HPV-16 DNA, Frazer bases additional arguments for conception based on alleged introductions into the United States of what Frazer urges are complete and enabling descriptions of the invention. (Paper 198 at 27.)

32. As a first instance of alleged conception in the United States, Frazer urges that Dr. Frazer introduced a complete description when he faxed the Zhou abstract (FX 1358) to the United States no later than 15 April 1991, which is said to have been the deadline for submitting abstracts for the Seattle Papillomavirus Workshop held in Seattle, Washington, in July 1991. (Paper 198 at 27-28.)

33. As a second date of alleged conception, Frazer relies on 17 May 1991, when Dr. Stenzel, the electron microscopist who did the electron microscopy for Drs. Frazer and Zhou, entered the United States with a complete understanding of the invention. (Paper 198 at 28.)

34. According to Dr. Stenzel, she had read a manuscript (FX 1249) that was subsequently published as *Zhou 1991*, that included electron micrographs that she had made; and that she understood the invention on the basis of that manuscript. (Paper 198 at 28-29; Stenzel declaration, FX 1247 at 29-31, ¶ 64.)

35. Frazer offers as a third date of alleged conception the introduction of a manuscript of *Zhou 1991* ("Zhou first draft," FX 1249) into the United States on 21 May 1991, evidenced by receipt of the Zhou first draft by the journal Virology (FX 1250.)

36. The authors listed on the manuscript are Jian Zhou (an inventor for Frazer), Xiao Yi Sun, Deborah J. Stenzel, and Ian Frazer (the other inventor for Frazer). (FX 1249 at 1.)

37. A receipt indicates that the editorial office of Virology is located in San Diego, California. (FX 1250.)

38. On 19 June 1991, Arnold Berk ("Berk"), the editor of Virology, sent a letter and comments from two reviewers on the Zhou first draft.

39. Berk writes that the work is "interesting," and that the paper "is in principle appropriate for publication in VIROLOGY." (FX 1251 at 1.)

40. In particular, Berk writes that:

> both reviewers suggest some modifications of the paper which I agree will be necessary before publication. Reviewer #1 feels that it is critical to show that both L1 and L2 proteins are expressed in the pLC201vv infected cells by using an immunological assay. Similarly, expression of E4 protein must be directly demonstrated before you can conclude that its expression does not affect assembly of the virion-like particles.

(FX 1251 at 1; emphasis added.)

41. Frazer submits a letter dated 9 July 1991, in which Dr. Frazer responds to the reviewer's comments and submits a manuscript revised to address the comments. (FX 1252.)

42. Dr. Frazer writes, "[w]e agree with the referee that it is important to demonstrate protein production in the cells and proteins in the virus-like particles." (FX 1252 at 5.)

43. Dr. Frazer writes further that they incorporated into the manuscript immunoprecipitation data showing that L1 and E4 protein were produced in the infected cells. Moreover, although they could not prove that L2 protein had been produced, they demonstrated that "L2 mRNA" (L2 messenger RNA) was produced in the infected cells. Dr. Frazer writes, "We accept that there is no proof from our work that L2 is a component of the virus like particles, although we have shown that it is necessary for their assembly, and we have been careful to word the title, abstract, and discussion of the paper to reflect this." (FX 1252 at 5.)

44. Inspection of the revised Zhou manuscript (FX 1252 at 6-25) shows that captions for figure 2 (showing the L1 and E4 analyses), figure 3 (L2 mRNA data), and figure 5 (cesium chloride equilibrium density gradient sedimentation of HPV-16 empty capsids and a transmission electron micrograph of an empty capsid), and associated text have been added to the manuscript. (FX 1252; the exhibit does not include copies of any figures.)

45. Frazer has not directed our attention to a receipt of the revised Zhou manuscript other than a letter from Paulette Wank, in the editorial office of Virology, dated 25 July 1991, informing Dr. Frazer that the revised manuscript had been accepted for publication. (FX 1253.)

46. Frazer offers as a fourth date of alleged conception the entry of Dr. Frazer into the United States on 19 July 1991 to attend the Seattle Workshop. (Paper 198 at 30, *citing, inter alia*, FX 1359 at 2; FX 1361 and FX 1362.)

47. As a fifth date of alleged conception, Frazer relies on Dr. Frazer's disclosure at his oral presentation to the Papillomavirus Workshop conference on 22 July 1991. (Paper 198 at 32, citing various declarations by conference participants, and referencing the discussion of the contents of the Frazer presentation at Paper 198, 8-18.)

48. Finally, Frazer submits that 26 July 1991, the last day of the Workshop, stands as another date by which Dr. Frazer or Dr. Zhou had communicated the complete invention to Schlegel, Lowy and Rose inventors who are involved in these interferences. (Paper 198 at 32.)

49. Frazer relies on *Gen. Talking Pictures Corp. v. American Tri-Ergon Corp.*, 96 F.2d 800, 810, 36 USPQ 428, 437 [sic: 438] (3d Cir. 1938), for the proposition that the date of

entry into the United States of a person to whom a complete conception has been communicated, or of the person who had the complete conception, qualifies as a date of conception. (Paper 198 at 27 and 30.)

50. Frazer also urges, in the alternative, that it was first to conceive and that it was diligent from a time before Schlegel's accorded benefit date of 25 June 1992, through Frazer's [constructive] reduction to practice on the filing date of its PCT application on 20 July 1992 (Paper 198 at 26).

51. Finally, Frazer argues that it was first to reduce the invention to practice by filing its PCT application, because Schlegel's application did not enable the production of virus-like particles and hence is not a constructive reduction to practice of the Count. (Paper 198 at 26.)

The state of the art and Frazer's inventive activities

52. Dr. Frazer characterized the state of the art circa October 1990, when Dr. Zhou arrived at Dr. Frazer's laboratory in Australia to conduct his postdoctoral studies, in several statements:

> 53. Dr. Zhou and I together thought of making papillomavirus ("PV") virus-like particles ("VLPs"). I was aware that Dr. Zhou had the technical skill to do the long polymerase chain reaction ("PCR") work necessary to clone the capsid protein genes of PV into vaccinia, at that time a rather unusual accomplishment. The length of the sequence that had to be amplified to

> clone the capsid protein genes of PV into vaccinia was close to the limit of what PCR technology allowed at the time. [Frazer declaration, FX 1277 at 2, ¶ 6; emphasis added.]
>
> 54. We thought it probable that HPV genotypes would likely be serotypes, i.e., that HPV-16 VLPs would work as a vaccine only against human papillomaviruses and possibly only against HPV-16 infection, as one PV infection did not protect against infection with another type. Thus, it would not be useful to test HPV-16 VLPs against antibodies to, or in animal models of, other PV types. [FX 1277 at 4, ¶ 11.]
>
> 55. We recognized that our yield of VLPs with the vaccinia virus system was small (this was a recognized problem with vaccinia virus) and that there would be potential problems for human studies because of concerns about the safety of vaccinia-expressed protein (this was being debated for vaccinia-based HIV vaccines at the time). [FX 1277 at 4, ¶ 13.]

56. Dr. Frazer states that they planned to express other L1 and L2 papillomavirus proteins using the baculovirus system. (FX 1277 at 5, ¶ 13.)

57. According to Dr. Frazer, Mr. Park, a graduate student under Dr. Frazer's direction, was already working with baculovirus to express papillomavirus capsid proteins. (FX 1277 at 5, ¶ 13.)

58. Dr. Frazer testified as to his own views about baculovirus expression of HPV-16 coat proteins and VLPs:

> Q So at the time the Australian application was filed, the priority case, you didn't believe baculovirus worked? [FX 1466 at 337, l. 17-19.]
>
> * * *

> A At the time that we filed the priority application, we had expressed L1 in baculovirus and had not got particles or not seen particles, and therefore it would be true at that time, yes. [FX 1466 at 338, ll. 8-11.]

59. As for the safety concerns with vaccinia, Dr. Frazer testified that a subsequent collaboration with Dr. Saveria Campo, a scientist working with bovine papillomaviruses in Scotland, could not proceed due to Scottish regulations against the vaccinia virus that Frazer was using to make synthetic BPV-1 virions:

> I wrote the facsimile [sent on or about 20 May 1992] to follow-up with Dr. Campo on discussions we had had at a scientific conference in Amsterdam. In the facsimile, I wrote that "we'd like to try inoculating cattle with our infectious synthetic BPV1 (L1+L2+plasmid) virions, to see if they get warts." I wanted Dr. Campo to inject cattle with synthetic BPV-1 virions that Dr. Zhou and I had made, to test their ability to be infectious. However, because of Scottish regulations against the use of vaccinia virus, we were never able to conduct these experiments.

(FX 1277 at 20, ¶ 51.)

60. Frazer states that there is no substantive difference between the work reported at the Seattle Papillomavirus Workshop in July 1991 and what is reported in the Australian application. (Deposition of Dr. Ian H. Frazer on 13 December 2004, FX 1466 at 109, l. 21, through 110, l. 2.)

61. As for what HPV-16 proteins were thought to be necessary to form virus-like particles in 1992, Dr. Frazer testified:

> A In contrast to other papillomavirus types from which we have direct evidence that L1 would be sufficient, at that time we still believed that L1 and L2 were necessary for HPV-16.
>
> Q And there was uncertainty at that point in time regarding which particular proteins would actually be necessary to produce HPV-16 VLPs?
>
> A That is correct. Well, there was – can I rephrase that? We believed that HPV-16 L1 and L2 were necessary, so I don't suppose there was uncertainty. That was what we believed.

(FX 1466 at 136, ll. 12-22.)

62. Dr. Frazer testified further:

> Q So if you would look at the state of the art objectively, looking back today, would you say that the state of the art was uncertain with regards to which proteins actually would be required to produce HPV-16 VLPs?
>
> A No, I think it would be fair to say that the state of the art was wrong.

(FX 1466 at 137, ll. 12-19.)

63. Frazer answered questions regarding the formation of viral capsids by HPV-16 as follows:

> Q . . . the work that you did suggests that HPV-16 in contrast to other PVs may be defective with respect to viral capsid formation.

A Yes, and that's what I – that's what – that wording is used by me elsewhere, and that is the wording that I would use. I still think that is an unproven hypothesis. It suggests that. It's neither proven one way or the other at this time because there are no authentic papillomaviruses of HPV-16 type isolated from anyone.

Q And you drew that conclusion based upon the lack of HPV-16 VLPs with the appearance of the authentic virus or virion?

A We drew that conclusion, first of all, because HPV virions of HPV-16 type had not been seen or purified, suggesting a problem with their – with their assembly and secondly, because the virus-like particles that we had produced were not identical to – morphologically identical, in other words identical in appearance, to papillomaviruses from BPV-1 or HPV-1, which were, if you like, the types available for – that you could derive from tissue and look at.

(FX 1466 at 139, l. 16, through 140, l. 15.]

64. Moreover, Frazer states that the immunological data in the provisional application "relates rather to production of L1 protein using antibody [sic]."

Q But nothing that would show an immune response in a patient or in a mouse or some other subject?

A That is correct.

(FX 1466 at 112, l. 21, through 113, l. 4.)

65. Regarding the presence of conformational epitopes on the virus-like particles Dr. Zhou is said to have made, Dr. Frazer testified:

A We describe the linear epitopes. Clearly, you cannot use linear peptides to define conformational epitopes.

Q And you can't determine from that analysis whether or not the particles that you produced had, in fact, conformational epitopes.

A We can demonstrate that they produced antibodies which reacted with virus-like particles.

Q But whether or not those antibodies were recognized in linear or conformational epitopes, you can't tell by testing with CAMVIR-1?

A Or indeed by any other means.

Q So you can't tell from that testing whether or not the particles that you produced had the conformational epitopes of the native virus?

A In 1991, we could not, that is correct, because at that time, the reagents that would be needed to do that work were not available.

(FX 1466 at 119, l. 17, through 120, l. 12.)

66. As for the immunological properties of the VLPs, Frazer testified:

Q So if you had HPV-16 particles that did not have the same morphological appearance as other HPV or papillomavirus virions, would you expect that the HPV-16 VLPs that you had produced would act the same immunologically as native HPV-16 virions?

A I would expect that they would, yes.

Q Even if their appearance was not the same as HP – as other PV's?

A Yes, I would.

Q And why is that?

A Because, first of all, we didn't know what an HPV-16 virion would look like, so at that time, one perfectly legitimate statement would be that these HPV-16 virus-like particles looked like HPV-16 virions and, therefore, resemble immunologically the HPV-16 virion. Secondly, because we saw a regular array of capsomeres, and a regular array of capsomeres allows the display immunologically of the salient features of the virus.

(FX 1466 at 142, l.9, through 143, l. 5.)

67. Regarding serology diagnostics, Dr. Frazer testified:

A . . . at that time we had not observed any correlation between antibodies directed against linear L1 sequences and detected HPV infection, nor had anybody else. And therefore, we thought that the virus-like particles might be a better means of testing for an immune response induced by infection. [FX 1466 at 216, ll. 6-12.]

* * *

Q Did you do that with the HPV-16 produced in the vaccinia virus?

A No, because there were significant concerns about biosafety with the material produced from the recombinant vaccinia viruses, which precluded their use in the routine diagnostic lab. [FX 1466 at 216, l. 20, through 217, l. 3.]

68. Dr. Frazer also testified about the difficulty of performing tests evaluating antibodies raised by recombinantly produced virus-like particles:

> C127 is a cell line that is susceptible to transformation by BPV and can therefore be used as the basis of a neutralization assay for infectious BPV-1 virions. I wanted to use C127 to test the ability of antibodies raised against our BPV VLPS to neutralize BPV virions. This work was not in fact undertaken as the C127 cells sent to us had, in our hands, a high spontaneous rate of transformation precluding their use for transformation assays.

(FX 1277 at 19, ¶ 49.)

III. Discussion

A prima facie case of derivation is made out if the moving party demonstrates that it conceived and communicated an enabling description of the invention to the opponent prior to the opponent's conception of the invention. *Hedgewick v Akers*, 497 F.2d 905, 908, 182 USPQ 167, 169 (CCPA 1974). Thus, to prevail in this interference on the basis of derivation, Frazer must prove that it conceived the invention and that it communicated that conception to Schlegel before Schlegel had conceived the invention. Proofs of conception, as part of a proof of derivation, may be supported by evidence of activities occuring outside the United States. *Hedgewick*, 497 F.2d at 907, 182 USPQ at 168.

Alternatively, Frazer must prove that it reduced the invention to practice first, or that it conceived the invention prior to Schlegel and that it was diligent in its efforts to reduce the invention to practice from (1) a time prior to Schlegel's conception until (2) a reduction to practice. 35 U.S.C. § 102(g)(1). Because all of Frazer's actual reductions to practice occurred outside of the United States, Frazer must rely either on the filing dates of its Australian and PCT applications for conception and constructive reductions to practice, or on complete and enabling disclosures within the United States of such activities. 35 U.S.C. § 104(a).

The motions panel found, in the Decision on Preliminary Motions, that the technical disclosures in Frazer's Australian application (FX 1050) and in the article *Zhou 1991* (FX 1001) are substantially the same. (Paper 175 at 21-22, ¶ 72.a.) The two documents differ primarily in that the Australian application contains more expansive descriptions of the scope of the purported invention. We also found that the presentations made at the Seattle Papillomavirus Workshop were subsets of the Australian application or *Zhou 1991*. (Paper 175 at 94-95, ¶¶ 244 and 245; *see also* Dr. Frazer's admission to that effect, FX 1466 at 109, l. 21 through 110, l. 2.) Accordingly, we focus on the adequacy of the Australian application as evidence of conception

and reduction to practice in light of Frazer's additional evidence purporting to prove that "wild-type," *i.e.*, assembly-efficient HPV-16 L1 DNA, was used to make the particles reported in the Australian application.

Because we conclude that Frazer has failed to prove legal conception of an embodiment within the scope of the Count on the basis of the Australian application, we need not consider separately whether the first Zhou manuscript or the presentations in Seattle, which are less complete disclosures, are adequate to establish conception. Frazer has not argued conception or actual reduction to practice based on any other evidence prior to the filing of its PCT application. Therefore, we need not consider Frazer's argument that it was reasonably diligent in its efforts to reduce to practice an embodiment within the scope of Count 2. However, we demonstrate that even if Frazer had established an earlier date of conception that was not an actual reduction to practice, it has failed to prove reasonable diligence by acts in the United States from any alleged date of conception through a reduction to practice.

Conception

Conception is "'the formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is thereafter to be applied in practice.'"

Burroughs Wellcome Co. v. Barr Labs. Inc., 40 F.3d 1223, 1228, 32 USPQ2d 1915, 1919 (Fed. Cir. 1994)(citations omitted). Conception requires both the idea of the invention's structure and possession of an operative method of making it. *Oka v. Youssefyeh*, 849 F.2d 581, 583, 7 USPQ2d 1169, 1171 (Fed. Cir. 1988). More than a hope, or wish, that a thing have certain desired properties, or that a process yield certain desired results, is necessary to establish a complete conception. At what point does the hope that is a basis for a research plan become a complete conception? The Federal Circuit has indicated that one way to distinguish a "bare hope" from a "complete conception" is to focus "on whether the inventors had a reasonable expectation that they would produce the claimed invention." *Hitzeman v. Rutter*, 243 F.3d 1345, 1358, 58 USPQ2d 1161, 1170 (Fed. Cir. 2001). According to the Federal Circuit, "[c]onception is complete only when the idea is so clearly defined in the inventor's mind that only ordinary skill would be necessary to reduce the invention to practice, without extensive research or experimentation." *Burroughs Wellcome*, 40 F.3d at 1228, 32 USPQ2d at 1919 (Fed. Cir. 1994) (citations omitted). The Federal Circuit has explained that the threshold for proof of conception should not be *de minimus* because:

> [t]he difficulty that would arise if we were to hold that a conception occurs when one has only the idea of a compound, defining it by its hoped-for function, is that would-be inventors would file patent applications before they had made their inventions and before they could describe them. That is not consistent with the statute or the policy behind the statute, which is to promote disclosure of inventions, not of research plans.

Fiers v. Revel, 984 F.2d 1164, 1169, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993), quoted in part in *Hitzeman*, 243 F.3d at 1357, 58 USQ2d at 1169.

Finally, the conception must be supported by evidentiary proof that the mental act of invention occurred on a certain date. "Because it is a mental act, courts require corroborating evidence of a contemporaneous disclosure that would enable one skilled in the art to make the invention." *Burroughs Wellcome*, 40 F.3d at 1228, 32 USPQ2d at 1919 (citation omitted).

Foreign inventive activity

Frazer's involved 928 application was filed on 19 January 1994. (FX 1063 at 1.) Accordingly, the following portion of 35 U.S.C. § 104(a) (1993)[3] applies to Frazer's applications:

> In proceedings in the Patent and Trademark Office, in the courts, and before any other competent authority, an applicant for a patent, or a patentee, may not establish a date of invention by reference to knowledge or use thereof, or any other activity with respect

[3] 35 U.S.C. § 104(a) (1993) applies to all patent applications filed on or after 8 December 1993 (Pub. L. 103-182); 35 U.S.C. § 104 (1994) applies to all patent applications filed on or after 1 January 1996 (Pub. L. 103-465).

> thereto, in a foreign country other than a NAFTA country, except as provided in sections 119 and 365 of this title.

Dr. Frazer testified that all of the experimental work with respect to HPV reported in its Australian and PCT applications was performed in Australia. (FX 1466 at 287, l. 19, though 290, l. 6.) Thus, as Australia is not a NAFTA country, activities in that country can be used to establish a date of invention only to the extent that they are described in Frazer's Australian application in fulfillment of 35 U.S.C. § 119, or in Frazer's PCT application in fulfillment of 35 U.S.C. § 365. Although we have not accorded Frazer the benefit of §119, we have accorded it the benefit of §365.

Frazer argues that the Australia-United States Free Trade Agreement ("FTA") requires each country to give "treatment no less favorable" to the other nationals as it does its own. This argument is not persuasive. First, the "no less favorable" provisions do not require either country to change a statute such as § 104. Section 104 distinguishes inventors based on where they were when they made their invention, not on the basis of their citizenship. The only exception provided by §104 is for inventors who are domiciled in the United States or a NAFTA country who invent something while "serving in any other country in connection with operations by or on behalf of the United

States or a NAFTA country." 35 U.S.C. § 104(a) (1993). In any event, the FTA entered into force on 1 January 2005[4], and there is no indication that its provisions are retroactive.

As Frazer recognizes, a corroborated communication into or within the United States that describes inventive activities produces knowledge of the invention in the United States, and thus can establish a date of invention as of the date of the communication. *E.g., Scott v. Koyama*, 281 F.3d 1243, 1247, 61 USPQ2d 1856, 1858 (Fed. Cir. 2002). Frazer relies on its Australian and PCT applications and, in the alternative, on communications into and within the United States as evidence of conception and reduction to practice of its invention.

Count Construction

The Count is defined by Frazer claims 65, 67, or 97, and Frazer urges that it has proved conception of an invention within the scope of each of these claims in the first Zhou draft (FX 1249) (Paper 198 at 6-9), the Frazer and Zhou presentations in Seattle (Paper 198 at 15-18), and (for claims 65 and 67 only) in the Zhou abstract (Paper 198 at 18-23). None of these claims[5]

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[4] Press release, Office of the United States Trade Representative, at http://www.ustr.gov/Document_Library/Press_Releases/2005/January/Lmark_U.S.-Australia_Free_Trade_Agreement_Goes_Into_Effect_Today.html (Copy attached.)

[5] We are mindful of the distinction between counts and claims, and use the term "claim" here merely as a convenient abbreviation for "alternative definition of the count." *Case v. CPC Int'l, Inc.*, 730 F.2d 745, 749, 221 USPQ 196, 199 (Fed. Cir. 1984) ("[t]he purpose of a count is to determine what evidence is

expressly recites properties required of the recited virus-like particles. In the Decision on Preliminary Motions, we considered at length what properties are required for these claims to cover compositions of matter and processes of making and using such compositions to be useful within the meaning of 35 U.S.C. § 101. (*E.g.*, Paper 175 at 67-68 (discussing the alleged usefulness of the HPV-16 particles in the context of the enablement requirement.) Frazer does not dispute that the claimed virus-like particles must have virion conformational epitopes in order to be useful: rather, Frazer urges that the HPV-16 particles disclosed in its Australian and PCT applications have them.

Throughout this interference, Frazer has insisted that all of the virus-like particles reported in its Australian application and in its involved application (which is identical to its PCT application) have conformational epitopes of the native virions. (*E.g.*, Frazer Opposition 2, Paper 62 at 18, urging that the Australian application teaches virus-like particles having conformationally correct epitopes.) For its part, Schlegel has consistently argued that such epitopes are a requirement for useful virus-like particles. (*E.g.*, Schlegel preliminary motion 2, Paper 22 at 16.) Accordingly, the

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relevant to the issue of priority.")

following construction of Frazer claims 65, 67, and 97 is not inconsistent with the positions adopted by the parties.

Frazer claim 97 requires the production of antibodies in the animal that is exposed to the papillomavirus virus-like particles. With regard to Frazer claim 97, we note that Frazer testified that "[t]here are significant exceptions to that, but in general, you get – when you introduce a protein with the appropriate adjuvant, you will get an antibody response." (FX 1466 at 215, ll. 16-19.) Frazer also stated that "at that time we had not observed any correlation between antibodies directed against linear L1 sequences and detected HPV infection, nor had anybody else. And therefore, we thought that the virus-like particles might be a better means of testing for an immune response induced by infection." (FX 1466 at 216, ll. 6-12.) Taken together, we understand these statements as indicating that the purpose of forming virus-like particles was to obtain L1 protein (or, in the case of HPV-16, L1 and L2 protein) in a conformation that mimicked the conformation of the L1 protein in the native virion closely enough that antibodies raised against the virus-like particles would also recognize the native virions. Such a recognition would be useful for determining exposure to the native virion, *i.e.*, for diagnosis.

Claims 65 and 67 cover papillomavirus virus-like particles made by a recombinant process, and that process of making them, respectively. Neither claim contains a recitation of a property or intended use that would require the virus-like particles to have any particular property. Both claims exclude HPV-16 as the source of the L1 capsid protein. However, the only disclosed utilities for virus-like particles are as diagnostic reagents and for immunization. Both of these utilities require the presence of conformational epitopes on the virus-like particles that are the same as conformational epitopes on the capsids of native virions. We note, however, that a conformational epitope on a virus-like particle need not be recognized by a neutralizing antibody in order for the virus-like particle to be useful as a diagnostic reagent, as long as the conformational epitope is recognized by an antibody to the native virion.

Effect of the Decision on Preliminary Motions on Conception

The motions panel held, in the Decision on Preliminary Motions, that Frazer was not entitled to the benefit for priority of its Australian application. (Paper 175 at 68, 128.) In the language of the regulations now in force, the Australian application was held not to provide a constructive reduction to practice of the invention, *i.e.*, it did not provide a described

and enabled anticipation under 35 U.S.C. § 102(g) of the subject matter of the count. Bd.R. 201 (37 CFR § 41.201 (2004))[6].

Frazer has introduced new evidence into the record regarding the identity of the HPV-16 DNA that was used in the experiments described in the Australian and PCT applications. As we explained elsewhere (Paper 194), that new evidence cannot be used to change our decision on preliminary motions, which was made on the record before us at that time. However, the new evidence, if persuasive, may compel us to find, on the record before us today, that Frazer has proven conception based on its Australian application, the manuscript of the *Zhou 1991* publication that was submitted to a journal office in the United States, or any of the presentations made at the Seattle Papillomavirus Workshop. There is nothing "inconsistent" in reaching a different, even diametrically opposed, conclusion on the basis of different evidence.

Accordingly, we turn to a consideration of the factual bases for determining whether, and if so when, Frazer established a "reasonable expectation that it would produce the claimed invention" prior to the filing of its PCT application.

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[6] The change in language from earlier definitions in now-discontinued 37 CFR § 1.601 et seq. (2004), "represent a clarification of, rather than a change to, the current practice." 69 *Fed. Reg.* 49960, 49990 (2004).

General technical factors underlying Frazer's alleged conception

The development in the 1980s of recombinant technology had given rise to the hope that viral vaccines could be made that had essentially no risk of viral infection because the viral proteins could be administered free of any viral nucleic acid. As of the 1991 filing date of Frazer's Australian application, there appear to have been only a few reports of such "subviral" vaccines. In the present record, there are only a small number of reports of other viral coat proteins that had been synthesized by recombinant techniques that showed promise as anti-viral vaccines. Dr. Frazer testified that human hepatitis B vaccines had been prepared from virus-like particles made using hepatitis B surface antigen (HBsAg) produced in a recombinant yeast cell culture. (FX 1277 at 3, ¶ 8, citing *McAleer 1984*[7] (FX 1137).)

[7] William J. McAleer et al., *Human Hepatitis B Vaccine from Recombinant Yeast*, 307 *Nature* 178 (1984). The original production of such VLPs was the subject matter of the interference *Hitzeman v. Rutter*, 243 F.3d 1345, 58 USPQ2d 1161 (Fed. Cir. 1994).

Also of record are reports of vaccines from parvovirus virus-like particles, *Kajigaya 1991*[8] (FX 1118), and *Brown 1991*[9] (FX 1142). According to these reports, virus-like particles ("capsids") were obtained when host cells were infected with recombinant viruses producing VP2, the major coat protein, or VP2 and VP1 (the minor coat protein). (FX 1118 at 4648, col. 1, last paragraph; FX 1142 at 2703, col. 2, first paragraph.) No virus-like particles were observed when only VP1-recombinant viruses were used. (*Id.*) According to Kajigaya, empty capsids containing VP2 alone or VP1 and VP2 raised antibodies in rabbits, but only rabbits inoculated with capsids containing both VP1 and VP2 raised neutralizing antibodies. (FX 1118 at 4648-49.)

Not all reports of recombinant proteins for sub-viral vaccines reported that the proteins assembled into structures similar to the native virions. Dr. Frazer also cited the production of bluetongue virus capsid proteins via a baculovirus expression system for vaccines as a way to avoid concerns about the safety of vaccinia-expressed proteins such as the ones

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[8] Sachiko Kajigaya et al., *Self-Assembled B19 Parvovirus Capsids, Produced in a Baculovirus System, are Antigenically and Immunogenically Similar to Native Virions*, 88 *Proc. Nat'l Acad. Sci. USA* 4646 (1991). The record copy bears a date stamp on the cover of the journal, "LIBRARY/JUN 4 1991/National Institutes of Health."

[9] Caroline S. Brown et al., *Assembly of Empty Capsids by Using Baculovirus Recombinants Expressing Human Parvovirus B19 Structural Proteins*, 65 *J. Virology* 2702 (1991). The record copy appears to bear a date stamp on the cover of the journal from the Dahlgren Memorial Library, "APR 22 1991."

produced by Zhou. (FX 1277 at 4, ¶ 13, citing *Roy 1990*[10] (FX 1117).) According to *Roy 1990*, full protection of sheep against "virulent virus challenge" was afforded by two successive injections of VP2 protein, the major coat protein of the bluetongue virus. (FX 1117 at 2002, first full paragraph.) Co-injection of a smaller dose of VP2 and VP5, the second outer capsid protein, also protected the sheep. (*Id.*) Roy speculated that "[i]t is possible that VP5 enhances the immune responses indirectly by interaction with VP2 and by affecting the conformation of VP2 and, consequently, its serological properties. (*Id.*) Neither Dr. Frazer nor *Roy 1990* appear to state whether Roy had obtained VLPs from the bluetongue virus capsid proteins.

On this record, we conclude that it was known that, in cases where the native viral coat is comprised of more than one protein, which proteins were present could affect whether a virus-like particle would be formed. We find further that it was known that conformations of the proteins in the virus-like particle could be affected by which proteins were present. However, it does not appear that the art had progressed sufficiently to make reasonably accurate predictions of which

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[10] Polly Roy et al., *Recombinant Virus Vaccine for Bluetongue Disease in Sheep*, 64 *J. Virology* 1998 (1990).

proteins would be required to form virus-like particles having virion conformational epitopes using species of viruses that had not been tested.

Although papillomaviruses had been studied for many years, including several structural studies by electron microscopy (*e.g., Finch 1965*[11] (FX 1051)), many properties of papillomaviruses were still poorly and only partially understood. HPV-16 viruses had been associated with the development of cervical cancer, and consequently had been investigated extensively. Although the HPV-16 DNA had been characterized sufficiently to distinguish it from other papillomavirus types, Frazer testified that the native virion had never been (and still has not) been observed. (FX 1466 at 140, ll. 1-2.) Frazer's Australian application noted that VLPs of HPV-16 had been observed in a cervical cell line that terminally differentiated in a murine (mouse) environment. (FX 1050 at 16, citing *Sterling*[12]; FX 1001 at 255.) *Sterling* reports that the virus-like particles were 50-nm in diameter (FX 1032 at 6306, Fig. 2, and 6307). Dr. Frazer testified that the electron micrographs of the particles "are [not] presented at such a resolution that it

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[11] J.T. Finch and A. Klug, *The Structure of Viruses of the Papilloma-Polyoma Type III. Structure of Rabbit Papilloma Virus*, 13 *J. Mol. Biol.* 1 (1965).

[12] Sterling et al., *Production of human papillomavirus type 16 virions in a keratinocyte cell line*, 64 *J. Virol.* 6305 (1990) (FX 1032).

could be established that they looked like other HPV and BPV virions." (FX 1466 at 144, l. 22 through 145, l. 4) The figures in *Sterling* that are said to show 50-nm virus-like particles are indeed rather obscure. (FX 1032 at 6306, Fig. 2.) Thus, there does not appear to have been any detailed prior reports of the morphology of the HPV-16 virion.

Dr. Frazer also testified that the cloning of the papillomavirus L1 genes was not routine, and that it required high technical skill. Indeed, according to Dr. Frazer, it was, in 1991, "a rather unusual accomplishment," that was "close to the limit of what PCR technology allowed at the time." (FX 1277 at 2, ¶ 6.) Moreover, Frazer recognized that testing the immunological properties of HPV-16 virus-like particles most likely could not be done with antibodies to other papillomavirus types due to the specificity of HPV genotypes. (FX 1277 at 4, ¶ 11.) Frazer also knew that there were experimental difficulties with the expression system it chose to work with: vaccinia, according to Frazer, was recognized to have low levels of protein production. (FX 1277 at 4, ¶ 13.) Furthermore, Frazer knew that vaccines trials with its products would be difficult due to concerns about the safety of vaccinia based vaccines. (FX 1277 at 4, ¶ 13; FX 1466 at 216, l. 20, through 217, l. 3.) Indeed, such safety concerns, embodied in

Scottish regulations, are said to have halted a collaboration with Dr. Campo, a scientist working in Scotland, in which the efficacy of certain virus-like particles at raising neutralizing antibodies was to be studied. (FX 1277 at 20, ¶ 51.) Experimental work in this area appears to have been far from routine.

Frazer's activities

On 21 May 1991, a manuscript (FX 1249) from Frazer's research group describing "virus-like particles" prepared recombinantly using HPV-16 genes was received by the journal *Virology* in San Diego, California (FX 1250). Dr. Frazer and Dr. Zhou, the Frazer inventors, and two others, were listed as the authors. Reviewer's comments on the article were sent to Frazer on 19 June 1991 (FX 1251), and on or about 9 July 1991, a revised version of the manuscript (FX 1252 at 6-25)) was sent to the journal (FX 1252 at 4-5). The article was accepted for publication on 25 July 1991 (FX 1253), and was published (mailed to subscribers) on 11 October 1991 (FX 1011 at 1; FX 1001, *Zhou 1991*.)

On 11 June 1991, Dr. Frazer sent a letter (FX 1232) to Dr. Roslyn A. Brandon, who was then a Business Manager, Biological and Health Sciences, for UniQuest Ltd., which is said to be the commercial arm of the University of Queensland (FX 1234, Brandon

declaration, ¶ 2). In the letter, Dr. Frazer requested that a "provisional patent" be filed based on the work reported in the Zhou manuscript, with Dr. Jian Zhou, Dr. Xiou-Yi Sun, and Dr. Ian Frazer as the inventors. On 19 July 1991, the provisional patent application was filed in the Australian patent Office for the University of Queensland and given the number PK 7322 (FX 1050).

The work reported in the Zhou manuscript and in the application appears to be the first reports of particles comprised of coat protein from a papillomavirus obtained by recombinant techniques. Frazer reported that "[t]he diameter of the virus-like particles purified from the infected CV-1 cells[13] varied between 35nm and 40nm." (FX 1050 at 13.) In contrast, the diameter of known papillomaviruses was reported to be approximately "about 50 nm." (FX 1001 at 253, col. 2, first full paragraph.)

According to Frazer, it used HPV-16 L1 and L2 genes from a pHPV16 sample provided by Dr. Gissmann. (FX 1001 at 251.) At that time, according to Dr. Frazer, they believed they were using the same HPV-16 clone that had been sequenced by Seedorf[14] (FX 1031). (FX 1466 at 103, l. 18, through 104, l. 13.) The L1

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[13] CV-1 cells are epithelial cells from a monkey kidney. Stanley 3d declaration, FX 1048 at 10, ¶31).

[14] Klaus Seedorf et al., *Human Papillomavirus Type 16 DNA Sequence*, 145 *Virology 181 (1985).*

and L2 genes were incorporated into a single plasmid, pLC201, and the plasmid was then used to construct a recombinant virus, pLC201VV. CV-1 cells were infected with the recombinant virus, yielding particles. No particles were observed when CV-1 cells were infected with recombinant viruses having only the L1 or the L2 gene. (*Id.*) Moreover, when CV-1 cells were infected with two recombinant viruses having the L1 and the L2 genes, respectively, no particles were observed. (*Id.*) In each case, L1 protein or L2 mRNA was observed. (*Id.*)

On the basis of these experiments, Frazer believed that the L1 protein alone would not assemble into virus-like particles. Instead, Frazer believed that both the L1 and L2 proteins were required for the formation of HPV-16 VLPs. (FX 1466 at 136, ll. 12-15.) Moreover, Frazer thought that the L1 and L2 genes had to be expressed together from the same plasmid; it was not enough to provide the L1 and L2 genes separately. (FX 1050 at 13, ll. 3-12.) These conclusions about HPV-16 virus-like particles turned out to be incorrect (FX 1466 at 136, l. 12, to 137, l. 3), but Frazer had not discovered this fact by the time it filed its PCT application one year later on 20 July 1992. Dr. Frazer declined to characterize his group's beliefs in this regard as uncertain. Rather, he characterized those beliefs — and those of the art — as certain, but wrong in light of later

work showing that only L1 protein was necessary (e.g., *Kirnbauer 1992*[15] (FX 1013)). (FX 1466 at 136, ll. 20-22; at 137, ll. 13-19.)

Another instance of a conclusion based on experimental results that turned out to be wrong was the suitability of baculovirus as an expression system for L1 and L2 capsid proteins. Dr. Frazer testified that at the time the Australian application was filed, his research group did not think that baculovirus was a viable expression systems for papillomavirus VLPs: "we had expressed L1 in baculovirus and had not got particles or not seen particles." (FX 1466 at 338, ll. 9-10.) Nonetheless, Frazer instructed his Australian patent counsel to file the Australian application, which contains no cautions against baculovirus, and indeed includes it as an example of a useful expression system. (Instruction letter, FX 1232 at 1-2; see also the Australian application, FX 1050 at 7, ll. 8-25.)

Some time after the Australian application was filed, it appears that Dr. Frazer told his Australian patent counsel about the negative results that one of his Ph.D. students (Park) had obtained with baculovirus. Nearly a year after the Australian application had been filed and a few days before the filing

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[15] Reinhard Kirnbauer et al., *Papillomavirus L1 Major Capsid Protein Self-Assembles into Virus-Like Particles that are Highly Immunogenic*, 89 *Proc. Nat'l. Acad. Sci. USA* 12,180 (1992).

deadline for Frazer's PCT application, Frazer's patent attorney sent a letter by facsimile to CSL, Frazer's real party-in-interest, including the statement:

> In relation to point 2, Dr Frazer confirmed that work now carried out has shown that commercial expression systems such as baculovirus have been tested but so far have proved deficient because of the fact that inter alia L1 and L2 may be glycosylated upon expression in the cytoplasm in the endoplasmic reticulum **and thus could not gain access to the cell nucleus so as to form a VLP**.

(FX 1289, paragraph bridging 1-2; bold added.) Dr. Frazer testified that, at the time the letter was written, a few days before the PCT application was filed, he no longer subscribed to the emphasized portion of the quote. (FX 1466 at 334-37, l. 4.) It appears that sometime between the filing of the Australian application on 19 June 1991 and the filing of the PCT application on 20 June 1992, Park had done further work that apparently indicated to Frazer that its earlier concerns were unfounded. (FX 1466 at 336-338.) Dr. Frazer had not, apparently, conveyed his changed opinion regarding the probable efficacy of baculovirus as an expression system to his patent counsel.

Frazer did not, in its applications or publications, characterize the immunological properties of the particles, except to conduct tests showing that L1 protein was indeed present in the particles. (FX 1466 at 112, l. 18, through 113,

1.4.) Dr. Frazer explained that neither electron microscopy nor x-ray crystallography were capable of determining the nature of conformational epitopes on the coat proteins of viruses. According to Dr. Frazer, one way to determine if an epitope on a virus-like particle is the same as an epitope on the native virion is "[b]y raising antibodies against the epitopes on the native [sic] VLP and the epitope on the native virus, demonstrating some sequence of homology across the range of antibodies and epitopes recognized." (FX 1466 at 41, ll. 9-13.) Dr. Frazer stated, however, it was impossible to determine, in 1991, whether the particles they produced had conformational epitopes of the native virions: "at that time, the reagents that would be needed to do that work were not available." (FX 1466 at 120, ll. 11-12.) Moreover, according to Dr. Frazer, subsequent work showed that even the choice of a cell line to explore the neutralization capability of antibodies raised by synthetic BPV-1 virions proved to be not a matter of routine, as the cell line underwent spontaneous transformation that prevented their use in assays for transformation induced by the viruses. (FX 1277 at 19, ¶ 49.)

Why were Frazer's HPV-16 virus-like particles significantly smaller (35 to 40 nm in diameter) than other papillomavirus VLPs (typically 50 nm in diameter), and why they were irregular

(rather than nearly spherical or icosahedral)? As reviewed at length in the Decision on Preliminary Motions (Paper 175 at 31-42), subsequent research by other groups indicated a plausible explanation.

Kirnbauer showed that the "prototype HPV16" DNA first isolated by Gissmann and coworkers has a single critical mutation that results in assembly-deficient L1 protein. *(Kirnbauer 1992* (FX 1013) and *Kirnbauer 1993*[16] (FX 1033). In Kirnbauer's hands, virus-like particles of L1 protein from the prototype HPV-16 could be made. Unlike the Frazer HPV-16 particles, the Kirnbauer particles from the "prototype" HPV-16 were about 50 nm in diameter and regularly shaped.[17] The prototype HPV-16 particles were, however, few in number compared to particles made recombinantly from BPV-1. According to a subsequent study by Kirnbauer, virus-like particles made from an HPV-16 L1 gene isolated from a less advanced lesion, were about 1000 times more plentiful than prototype particles, indicating that the mutation was responsible for the assembly-deficient character of the

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[16] Reinhard Kirnbauer et al., Efficient Self-Assembly of Human Papillomavirus Type 16 L1 and L1-L2 into Virus-Like Particles, 67 *J. Virology* 6929 (Dec. 1993).

[17] The differences of size and shape between the particles produced by Dr. Kirnbauer, using the recombinant baculovirus/Sf9 insect cell expression system and the particles produced by Dr. Zhou, using the recombinant vaccinia/CV-1 cell expression system remain unexplained on the present record.

prototype HPV-16 L1 protein. (FX 1033 at 6932-33.) Subsequent studies[18,19] indicated that the prototype HPV-16 L1 protein lacked conformational epitopes of the wild-type HPV-16 L1 protein in the native HPV-16 virion.

For more than a decade, it appears that the papillomavirus research community has accepted the Kirnbauer explanation of the small irregularly shaped particles produced by Frazer. Indeed, Frazer candidly admits that, "[t]hroughout the preliminary motions phase of this interference, Frazer and its witnesses were operating under the assumption that the working example in the Frazer provisional application used prototype HPV-16 L1. Therefore, certain papers and documents submitted in interferences 104,773, 104,775, and 104,776, have mistakenly stated that the working example used "prototype HPV-16 L1." (Paper 198 at 69.)

Throughout the present interferences, however, Frazer has maintained and continues to maintain that even the "incorrectly assembled" arrays of HPV capsomeres exhibited conformational epitopes of the native protein. According to Dr. Frazer:

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[18] Richard B.S. Roden et al., *Interaction of Papillomaviruses with the Cell Surface*, 68 J. VIROLOGY 7260 (1994). (FX 1038; SX 2013.)

[19] Richard B.S. Roden et al., *In Vitro Generation and Type-Specific Neutralization of a Human Papillomavirus Type 16 Virion Pseudotype*, 70 J. VIROL. 5875 (1996). (FX 1053; SX 2045))

"[b]ecause, first of all, we didn't know what an HPV-16 virion would look like, so at that time, one perfectly legitimate statement would be that these HPV-16 virus-like particles looked like HPV-16 virions and, therefore, resemble immunologically the HPV-16 virion. Secondly, because we saw a regular array of capsomeres, and a regular array of capsomeres allows the display immunologically of the salient features of the virus." (FX 1466 at 142, l. 19, through 143, l. 5.)

In the Decision on preliminary motions, we considered and rejected Frazer's argument that any particle formation indicated that the L1 protein had assumed the correct, native conformation. (See, *e.g.*, interference 104,776, Paper 175 at 61-62 and 66, discussing Frazer's protein folding theory. In interference 104,773, see Paper 197 at 54-64 and 114. In interference 104,775, see Paper 149 at 44-45.) To the extent that particle morphology reflects the atomic-level molecular conformation said to be characteristic of epitopes, it seems reasonable that the irregularly shaped small particles reported in the Australian application would be an indication that the conformation of the constituent L1 proteins is not that of the protein in native virions. We need not and do not draw that conclusion: but we do conclude that there is substantial reason to doubt the objective correctness of Frazer's proposition. Frazer has failed to come

forward with further evidence that the small irregular particles it reported in its Australian application actually had L1 protein having the conformation of native HPV 16 virions, and thus induced antibodies active against the native HPV 16 virions. Accordingly, we do not accept Frazer's renewed arguments in this regard.

Frazer has also insisted throughout this interference that the Australian application is enabling for the full scope of its claims, including those that define the count. Frazer has urged that the enablement is not limited to particular vectors or expression systems. (*E.g.*, Paper 198 at 69, "the Frazer provisional and PCT applications and 1991 Frazer and Zhou publications describe and enable PV VLPs.") Indeed, the Australian application describes the invention broadly, without restriction as to recombinant DNA molecules (including plasmids, cosmids, baculovirus, vaccinia virus, adenovirus, or retrovirus) or host cell, including prokaryotic systems (E. coli) as well as eucaryoties such as yeast, insect cells (S. Frugiperda), and mammalian cells. (FX 1050 at 6-7.) As the record now shows, however, at the time the Australian application was filed – and for some months afterwards – on the basis of experimental work by Park, Frazer thought that the baculovirus system would not work for VLP formation because the L1 and L2 proteins could not get to

the cell nucleus, where they were (and are) thought to assemble into virus-like particles. Thus, the preponderance of the evidence demonstrates that, when the Australian application was filed, the inventors had objective – although ultimately incorrect – evidence that their invention would not work with baculovirus embodiments. This fact weighs against Frazer having a reasonable expectation that it would produce virus-like particles having virion conformational epitopes.

Frazer has now come forward with new evidence and argument purporting to show that the genetic material that Dr. Zhou used in his original experiments reported in the Australian application, at the Seattle Papillomavirus Workshop, and in *Zhou 1991*, was actually a wild-type HPV-16 L1 DNA. (Paper 198 at 67.) Frazer presents testimony that, after the Decisions on Preliminary Motions in these interferences, it obtained the sequence of the DNA deposited in the American Type Culture Collection ("ATCC") identified in the PCT application as the L1 and L2 genes of HPV-16. (Paper 198 at 67, citing the testimony of persons representing themselves as CSL employees (FX 1236, FX 1417, and FX 1416) and as the officer in charge of the sequencing facility at the company that performed the sequencing (FX 1415).) Stanley testifies on behalf of Frazer, that the results (FX 1412) show that the sequence of the DNA used in the

Australian application was that of the "wild-type" HPV-16 virion, not the "prototype" HPV-16 virion. (Stanley 9th declaration, FX 1418 at ¶¶ 16.) Frazer asserts that therefore the Board's decisions denying that the Australian application did not provide a constructive reduction to practice for benefit for priority, and for lack of enablement, should be withdrawn. That is, Frazer argues that its Australian application stands as evidence of conception and constructive reduction to practice of an embodiment within the scope of the Count. (Paper 198 at 69-73.)

Frazer has not, however, directed our attention to any new or old immunological evidence in the record regarding the nature of the epitopes on the Zhou particles. Frazer testified that in 1991 they could not test the Zhou HPV-16 particles for the presence of virion conformational epitopes due to the lack of necessary reagents:

> Q So you can't tell from that testing whether or not the particles that you produced had the conformational epitopes of the native virus?
>
> A In 1991, we could not, that is correct, because at that time, the reagents that would be needed to do that work were not available.

[FX 1466 at 120, ll. 6-12.)

Even if we were to accept all of Frazer's representations about the HPV-16 DNA said to have been used by Dr. Zhou and reported in the Australian application and in *Zhou 1991*, there is

still no credible evidence that the Zhou HPV-16 particles have conformational epitopes of the HPV-16 virions. The small, irregularly shaped particles remain unexplained, and they remain as evidence that there is objective reason to doubt that useful particles were described by the Australian application. Frazer's new evidence and argument does not change the finding of the motions panel in the decision on preliminary motions:

> the record shows that even more than a decade after the Australian application was filed, it has not been shown definitively whether the prototype VLPs have conformational epitopes of the native virions. Stanley, Frazer's expert, testified:
>
> Q But at this point, one cannot predict whether or not the conformational epitopes of the intact virion are present on particles produced from the prototype?
>
> A I do not know of any evidence. The answer is I do not know.
>
> (FX 1128 at 229, ll. 5-10.)

(Paper 175 at 66.) Recombinant protein technology for vaccines was an extremely complex art. In 1991, the art was nascent, evidenced by the perhaps understandable incorrect conclusions noted supra, which were based on experimental evidence, even as to such relatively "simple" matters as which proteins were necessary to form virus-like particles, and whether baculovirus was a suitable system for papillomavirus coat protein expression. Revising hypotheses in the face of evidence is a hallmark of

well-conducted research. Even experts testifying on behalf of Frazer state that they are still unable to predict the existence of virion conformational epitopes on virus-like particles. In light of these findings, we hold that the preponderance of the evidence indicates that, although there may have been great hope, there was not a reasonable expectation that the goal of virus-like particles having conformational epitopes would be achieved, based on the small, irregularly shaped particles disclosed in the Australian application or any version of the Zhou manuscript.

Frazer did not prove conception

On the record before us, we conclude that Frazer has not established that the HPV-16 work reported in the Australian application or the *Zhou 1991* publication provided a reasonable expectation that it had produced, or would produce, a useful embodiment of the claimed invention, *i.e.*, a virus-like particle having conformational epitopes of the native virion. Certainly Frazer hoped that it had made such a particle. However, on this record it has not shown that the particles derived from its HPV-16 DNA, whatever the true source, had conformational epitopes of the native capsid protein. Conception requires more than a promising idea. The general idea of recombinant viral subunit vaccines was "in the air" and had been realized in a few instances, such as the hepatitis B particles at issue in

Hitzeman. As the motions panel explained in the decision on preliminary motions, the state and knowledge in the art showed that the mere existence of a particle that looks like the virion does not guarantee the existence of virion conformational epitopes on the particle. Frazer conceded as much. (FX 1466 at 40-42.)

Frazer has not offered further explanations of why the mere identity of the DNA as "wild type" establishes that the particles had the desired wild type conformational epitopes. We considered at length its arguments in the preliminary motions that the existence of virus-like particles proved the existence of conformational epitopes, and found them unpersuasive.

Dr. Frazer's argument that the existence of a "regular array of capsomers allows the display immunologically of the salient features of the virus" (FX 1466 at 143, ll. 3-5), even if true, does not prove that the "salient features" (epitopes) of the virus are in fact displayed. Frazer has not presented sufficient evidence or argument to persuade us that we should accept such an argument now.

Because the presentations at the Seattle meeting are at best cumulative with the Australian application and the *Zhou 1991* article, we hold that they do not suffice to establish conception. Accordingly, we find that Frazer could not have

communicated a complete conception of the invention to those in the audience, including the Schlegel inventors, at the Seattle meeting. Thus, we find that Frazer has failed to prove that Schlegel derived the invention from Frazer's disclosures at the Seattle meeting.

Additionally, we reject Frazer's arguments that the mere entry into the United States of a person having knowledge of the alleged conception suffices to establish a date of conception by Frazer. *Gen. Talking Pictures* does not support Frazer's legal theory. In that interference, DeForest sought to demonstrate conception of his invention via a note he wrote on 12 October 1918, and showed to his fellow passenger and patent attorney, Darby, while they were outside of the United States. DeForest initialed the note, as did Darby, who also wrote the letters "E&U" ("explained and understood") on the paper. DeForest testified that he placed the note in a book of poems and forgot about it until Darby requested any written data he had bearing on the interference. The passage on which Frazer appears to rely reads in full:

> There is evidence to indicate DeForest returned to the United States upon January 1, 1919, and this date the Board of Appeals held should be taken to be the date of his conception of the invention, since upon October 12, 1918, he was on the high seas upon a ship of British registry. Since it is the recognized practice in the United States Patent Office in cases of interference to

> allow a foreign inventor to claim as the date of his conception of an invention, the date upon which a letter sufficiently describing that invention is received in the United States, DeForest as a citizen of the United States certainly must be put in no worse position than a foreign inventor and we therefore hold that he is entitled to claim January 1, 1919, the first day of his re-entry into this country, as the date of his conception of the invention in question.

96 F.2d at 810, 36 USPQ at 438. Thus, the court put DeForest in the position of a foreign inventor whose letter describing the invention was received on a certain date in the United States. On these facts, it is the entry of DeForest's note into this country, in DeForest's possession, rather than the entry of DeForest himself, that puts DeForest on par with the letter-writing foreign inventor.

Thus, the mere entry of either Dr. Stenzel or Dr. Frazer into the United States, even if each one had a complete and enabled idea of the invention as it was to be used in practice, would be insufficient, without more, to prove conception.

Diligence

A party may prevail in an interference even if it was the last to reduce to practice, if it was the first to conceive and if was reasonably diligent "from a time prior to conception by the other." 35 U.S.C. § 102(g). Schlegel filed its original application on 25 June 1992, and is the senior party.

Frazer's date of reduction to practice is 20 July 1992. Even if we were to hold that Frazer had conceived an embodiment within the scope of Count 2, we find that the activities in the United States offered by Frazer in support of diligence are not sufficiently continuous throughout the critical period to establish reasonable diligence.

Frazer urges that it was the first to file an application "disclosing embodiments of the count" (Paper 198 at 34, referring to the Australian application). We have rejected this proposition to the extent that it refers to a complete conception or a disclosure of an actual or constructive reduction to practice. Indeed, if Frazer had been accorded the benefit for priority of the Australian application, *i.e.*, had we considered it to provide a complete and enabling description of an embodiment within the scope of the count, no proof of diligence would be necessary as against any of Frazer's opponents in interferences 104,773, 104,775, and 104,776.

Even if we were to hold that Frazer had conceived the invention (without a simultaneous reduction to practice), we would reject Frazer's argument that it was reasonably diligent between the date of its conception and the date of its constructive reduction to practice when its PCT application was filed. (Paper 198 at 34-64.) Frazer argues that its efforts to

secure a partner for vaccine testing and production and its efforts to deposit biological samples with the ATCC involve activities in the United States, and are therefore not subject to the strictures of 35 U.S.C. § 104. Moreover, Frazer urges that 35 U.S.C. § 363 and the Australia-United States Free Trade Agreement support the crediting of Frazer's efforts in Australia to prepare the PCT application to Frazer's diligence. (Paper 198 at 37-39.)

As we have already indicated, the plain language of 35 U.S.C. § 104 makes clear that the only ways foreign activities can be used to establish a date of invention is via a priority document (35 U.S.C. §§ 119 and 363), or if the inventor is domiciled in the United States or a NAFTA country and out of that country on behalf of that country. The language chosen and adopted by Congress does not distinguish between United States nationals and foreign nationals. Thus, if an American citizen not working on behalf of the United States, were listed as an inventor on Frazer's application, and all the work had been done in Australia, the result would be no different. As a matter of law, none of the foreign activity can be credited to Frazer's proof of priority of invention, including diligence, except for the benefit accorded Frazer of its international application designating the United States. 35 U.S.C. § 363.

Frazer relies on contacts with the ATCC as evidence of diligent efforts to reduce the invention to practice. Thus, on 13 October 1991, the ATCC is said to have received deposit forms sent by Frazer a couple of weeks before. Actual samples are said to have been deposited on 27 March 1992 (FX 1324 at 6), and on 3 April 1992 (FX 1324 at 4). Facsimile transmissions related to the deposit arrangements were sent between Frazer and ATCC on 17 and 31 December 1991, 21 January 1992, 26 March 1992, and on 1-9, 22, and 30 April 1992.

The first reported efforts by CSL, Frazer's real party in interest, to find potential United States parties to make and test vaccines occurred in July and August 1991 (Ostrow; FX 1336) and in September 1991 (Reichmann, FX 1337). Frazer also reports letter and facsimile contacts between Dr. Frazer and AMVAX, a vaccine company in Beltsville, MD, on 15 and 23 August 1991 (FX 1365, 1366), on 23 and 24 September 1991 (FX 1368, 1369, 1370), and on 1 October 1991 (FX 1371). The next reported effort began in June 1992, when Dr. Gust is said to have entered the United States on 16 June, and to have met with Merck officials on 19 June.

Schlegel's application was filed on 25 June 1992, the week after Dr. Gust is said to have met with Merck officials. No further activity in the United States is offered as evidence of

diligence prior to 20 July 1992, when the Frazer PCT application was filed. Thus, there is no evidence of activities in the United States between 25 June and 20 July 1992 that establishes reasonable diligence to a reduction to practice.

Even if all of these activities are credited to Frazer, a matter on which we do not rule, they are not sufficiently continuous throughout the critical period. Thus, they are not sufficient to establish diligence in the United States towards an actual reduction to practice.

Frazer's alleged first reduction to practice

Frazer urges that it was first to reduce an embodiment of the count to practice based on its Australian application. (Paper 198 at 64-73.) We have already rejected Frazer's arguments that it established an actual reduction to practice with the work reported on HPV-16 in the Australian application and the *Zhou 1991* publication.

Alternatively Frazer argues that it was first to reduce to practice because Schlegel's specification does not enable virus-like particles, which are required elements of Count 2. (Paper 198 at 64 and 73-84). Frazer does not argue and cites no evidence that Schlegel lacks a written description of recombinant virus-like particles. Indeed, Dr. Margaret Stanley ("Stanley"), testifying for Frazer, states, "[t]he [Schlegel] application

indicates, however, that this [virus-like particles] was one of their objectives." FX 1402 at 3, ¶ 11, citing the Schlegel application, FX 1015 (SX 2023) at 38, 40, and 48. Accordingly, Frazer's arguments stand or fall on the issue of enablement of virus-like particles by the Schlegel application. Frazer, as the moving party, bears the burden of proving lack of enablement.

Frazer notes that Schlegel's specification provides no working examples yielding virus-like particles of a papillomavirus. (Paper 198 at 74-76 and 77.) Frazer also urges that Schlegel's application "provides no direction or guidance on how to turn Schlegel's failure to VLPs into success." (Paper 198 at 78.) Frazer argues further that Schlegel's application actually teaches away from virus-like particles by teaching that they are not necessary. (Paper 198 at 78.)

Frazer urges further that the art, which it characterizes as the formation of papillomavirus virus-like particles, is represented by *Zhou 1991* (FX 1001), the Zhou abstract (FX 1002 at 380) and the Frazer presentation (FX 1005). Frazer urges further that because the Board held that these publications (and Frazer's Australian application) are not enabling, there is no advance in the art that can have provided the enablement missing from Schlegel's specification. (Paper 198 at 78.)

Frazer relies on the testimony of Stanley to establish that undue experimentation would have been required to make virus-like particles on the basis of Schlegel's application and what was known in the art as of Schlegel's filing date. Frazer discounts Schlegel's disclosure of the baculovirus-Sf9 (insect cell host) system as an alternative expression system to the SV40-COS expression system used by Schlegel. Stanley testified that, "[b]ecause the COS cell over-expression system failed to make HPV VLPs, the skilled artisan would have [had] no reason to expect that HPV VLPs could be made using the baculovirus over-expression system." (FX 1402 at 4, ¶ 14.) Stanley testified further that "extensive experimentation" would have been required to make virus-like particles. In particular, Stanley states that it would have been necessary to create a new plasmid expression system and to determine what host cell system to use, and to determine which papillomavirus L1 protein to express, and to determine what extraction method to use to recover and purify VLPs. (FX 1402 at 4-5, ¶ 14.)

Finally, Frazer argues that the Schlegel application does not enable conformational epitopes, urging that the decision on Frazer preliminary motion 4 was incorrectly decided. (Paper 198 at 80-84.)

Discussion

We previously considered the issue of Schlegel's enablement of virus-like particles in the context of Frazer preliminary motion 4, for judgment that Schlegel's claims were not enabled for their full scope. (Paper 175 at 109-11.) There, we considered and rejected Frazer's arguments that because Schlegel did not observe virus-like particles in its preparations, the L1 protein made by Schlegel did not have conformational epitopes. We also expressly rejected Frazer's arguments that Schlegel had not enabled the production of virus-like particles. (Paper 175 at 110.) Moreover, Frazer previously requested reconsideration of the Board's decision on Frazer preliminary motion 4. (Paper 181 at 13ff.) The original motions panel reconsidered its decision, but did not grant Frazer the requested relief. (Paper 194.) As Frazer has already had a full and fair opportunity to challenge that decision, we see no compelling reason to permit Frazer a third bite at that apple.

In any event, we do not see that Frazer has carried its burden of establishing that undue experimentation would have been required to make virus-like particles based on Schlegel's disclosure. Stanley does not explain why the alleged required experimentation would have been beyond the level of ordinary skill. Part of the problem is that Stanley does not indicate

what was the level of ordinary skill, nor does she explain what would have been the nature of the difficulties likely to have been encountered. Accordingly, we have no objective basis to evaluate her and Frazer's conclusion that the experimentation required to overcome those difficulties would have been "undue." It has long been settled that the necessity for experimentation, even extensive experimentation, does not signal "undue experimentation" if the work is routine. *See In re Cook*, 439 F.2d 730, 733, 169 USPQ 298, 300 (CCPA 1971) (mere amount of effort is not dispositive of lack of enablement).

Frazer's argument at oral hearing

At oral argument on 30 June 2005, Frazer urged that an opinion in the case of *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 75 USPQ2d 1297 (Fed. Cir. 2005), entered 27 June 2005, somehow supports Frazer's case for derivation. (Paper 261 at 210-11, 222-24.) Although motions panels do not ordinarily consider arguments at oral hearing that have not been briefed, the panel was familiar with that case and exercises its discretion to consider Frazer's arguments, particularly since *Rasmusson* was decided after principal briefing.

Frazer appears to argue that *Rasmusson* held that a disclosure that was not enabling under 35 U.S.C. § 112, first paragraph, for purposes of obtaining benefit under 35 U.S.C.

§ 120 of earlier filed copending applications, was sufficiently enabling to be applied as prior art under 35 U.S.C. § 102(b). (Paper 261 at 210.) The court, according to Frazer, explained that the difference is that a utility does not need to be disclosed in an anticipatory reference. (Paper 261 at 210.) Frazer then seems to argue that *Rasmusson*, which concerned anticipation under 35 U.S.C. § 102(b), applies to its derivation case, which arises under 35 U.S.C. § 102(f). (Paper 261 at 210-11 and 223.)

We confess that we do not fully understand Frazer's argument. In particular, it is not clear to us that *Rasmusson* involved evidence of derivation. Frazer's argument, which was necessarily brief, did not enlighten us on this issue. Nor has Frazer explained how the Federal Circuit's decision in *Rasmusson* indicates that the reasoning in that case should be extended to cases involving derivation, such as the one before us.

We do think it unlikely that the panel in *Rasmusson* contemplated that it was signaling a radical shift in the long-settled law that proof of derivation requires proof that there was a communication of the complete, enabled conception. *Agawam Co. v. Jordan*, 74 U.S. (7 Wall.) 583, 602-03 (1868) ("Suggestions . . . must have embraced the plan of the improvement, and . . . enabled an ordinary mechanic . . . to construct and put the

improvement in successful operation,"); *Hedgewick v. Akers*, 497 F.2d 905, 908, 182 USPQ 167, 169 (CCPA 1974) ("Derivation is shown by a prior, complete conception of the claimed subject matter and communication of the complete conception to the party charged with derivation."). Given the uncertainties of the applicability of *Rasmusson* to the facts of this case, we decline Frazer's invitation to extend *Rasmusson* to derivation.

Moreover, for reasons discussed at length in previous decisions and *supra*, we have held that Frazer did not disclose complete and enabled conceptions of the count at the Seattle conference. At oral argument, Frazer stated that the only additional evidence on conception that was not of record at the preliminary motions phase was the evidence that the HPV-16 L1 DNA was the wild-type DNA. (Paper 261 at 224.) As stated *supra*, this additional evidence does not prove the existence of virion conformational epitopes on the small, irregular particles described in the Australian application. In other words, the additional evidence does not prove that the conformational epitopes were inherent in those particles. Thus, unlike the situation in *Rasmusson*, this is not a case in which subsequent events have shown that the original disclosure actually had all of the limitations required by the Count. Thus, the facts of the present interferences seem to distinguish them from *Rasmusson*.

IV. Summary

For the foregoing reasons, on the record before us, we hold that Frazer has not carried its burden of proving prior conception, diligence, or prior reduction to practice of an embodiment of Count 2. Frazer is therefore left with the accorded benefit for priority of the filing date of its PCT application on 21 July 1992.

/ss/ Fred E. McKelvey
FRED E. McKELVEY, Senior
Administrative Patent Judge

/ss/ Sally Gardner Lane
SALLY GARDNER LANE
Administrative Patent Judge

BOARD OF PATENT APPEALS AND INTERFERENCES

/ss/ Michael P. Tierney
MICHAEL P. TIERNEY
Administrative Patent Judge

/ss/ James T. Moore
JAMES T. MOORE
Administrative Patent Judge

/ss/ Mark Nagumo
MARK NAGUMO
Administrative Patent Judge

Appendix: Technical Background for interferences 104,771 through 104,776

The following appendix is provided as an executive summary of the technical background underlying interferences 104,771 through 104,776. It is intended to be a convenient non-technical guide for those readers who are not familiar with the technology or the discussions in the Decisions on Preliminary Motions in the respective interferences. We have tried to keep it simple by not presenting the subtleties of the art or the points of disagreement. Those familiar with the art will recognize the oversimplifications. Moreover, we have not cited the record. Detailed findings of fact are set out throughout the decisions and opinions, which stand independently of this appendix. Although we believe this summary is accurate and consistent with the findings of fact and the conclusions drawn in the decisions and opinions, it is in no way a substitute for the detailed findings of fact.

Papillomaviruses

Papillomaviruses infect a wide variety of animals, typically giving rise to growths (warts) that may be painful or unsightly, but usually not malignant. The viruses are highly species and tissue specific. For example, the virus that gives rise to

plantar warts on the soles of the feet of human beings (HPV-1) will not infect other human tissues, such as oral membranes, or any tissue of any non-human animal. By 1990, more than 50 distinct human papillomaviruses had been identified on the basis of differences among their DNA sequences, usually determined by DNA-matching ("hybridization") experiments.

Certain human papillomaviruses give rise to ano-genital warts, and certain of these viruses have been established as causative agents of cervical cancer. The type 16 human papillomavirus ("HPV-16") was the first virus implicated as a causative agent of cervical cancer. HPV-16 was identified by extracting viral DNA from an advanced cervical tumor and comparing it to the DNA of other human papillomaviruses by hybridization experiments. Because it had a low degree of hybridization (*i.e.*, did not match) with other types, it was assigned a new type number, "16." Eventually, the DNA was sequenced, and samples were distributed to numerous laboratories around the world. This first isolated and sequenced HPV-16 DNA came to be called the "prototype HPV-16" DNA. The DNA of other HPV-16s and other papillomaviruses were also isolated and used in artificial genes to make virus proteins. Several other HPV types have also been implicated as giving rise to cervical cancer.

Papillomaviruses have a protein coat or shell made of two proteins, called "L1" and "L2." The L1 protein forms the outermost shell of the papillomavirus. The exact location of the L2 protein is not known, but it is thought to be in the interior of the shell.

Virus-like particles

When viruses infect cells, the viruses take over the cellular machinery and reproduce the viral DNA and all the proteins that make up the virus. The viral coat proteins often pack spontaneously around the viral DNA to form the mature viruses. Even in the absence of the viral DNA, the viral coat proteins may aggregate to form particles having the approximate size and shape of the native virus. Such particles, if they do not contain the viral DNA, are generally referred to as "virus-like particles."

We have not been directed to any evidence of reports of recombinantly-produced virus-like particles from papillomaviruses prior to the work at issue in these interferences.

Vaccines

The immune system can protect the body against invading viruses via antibodies to the outermost coat of the virus. Any

given type of antibody will bind only to a specific site having a particular molecular shape or "conformation." Antibodies that bind to specific sites, called "epitopes," on the surface of an intact virus, are said to bind to "conformational epitopes." If the antibodies bind to all the receptor sites on the virus that the virus uses to bind to cells, receptor sites will be blocked, and the ability of the virus to infect cells will be neutralized.

Antibodies are made by specialized cells. A given antibody-making cell makes antibodies that recognize only one specific epitope. When the individual is exposed to a particular virus, the cells that make the antibodies that recognize the protein coat of that virus will be stimulated to make more antibodies, and they will remember that virus. Upon future exposure to that virus, the individual's immune system will be prepared to make large quantities of those antibodies.

Vaccines work by priming the immune system to produce large numbers of neutralizing antibodies to particular viruses. In some cases, the patient can be exposed to a killed or weakened strain of the virus rather than the active virus itself. The process of killing or weakening the virus, however, may change the exposed surface of the virus so much that few antibodies to the active virus are activated. It is also possibile that the

killed or weakened virus may be re-activated, leading to infection and disease rather than immunization.

A gene is a DNA molecule that carries the genetic code that instructs the cell how to make a particular protein. Genetic engineering using so-called "recombinant" techniques involves "recombining" a foreign gene with the genes of a host cell. Then the machinery of the host cell is harnessed to make the protein coded for by the foreign gene. That protein can be made in large quantities, isolated, and purified. These recombinant techniques brought hopes that the coat proteins of viruses could be produced in large quantities, cheaply, easily, and completely free of viral DNA.

If the recombinant viral coat protein had the same conformational epitopes as the proteins in the native virus, it might serve as a vaccine. Because the protein would not be subjected to the process of weakening or killing the virus, it might be more effective at priming the immune system to make antibodies against the virus than vaccines made from viruses. Moreover, a vaccine made from such proteins would carry no risk of inducing the viral disease, such as cervical cancer. Given the tendency of many viral coat proteins to form virus-like particles, the virus-like particles, if they had the

conformational epitopes of the native virus, could also serve as vaccines.

Only a couple of reports of vaccines based on recombinantly produced virus-like particles appear in the record as "prior art" to the applications involved in these interferences. The most prominent example in the record of a prior-art recombinant viral coat protein vaccine is that for hepatitis-B, which was the subject of the interference reported in *Hitzeman v. Rutter*, 243 F.3d 1345, 58 USPQ2d 1161 (Fed. Cir. 2001).

Diagnostic reagents

In addition to uses as vaccines, recombinantly produced viral coat proteins having the conformational epitopes of the L1 protein of the native virus could also be used as diagnostic reagents to determine whether an individual had been exposed to a particular type of papillomavirus. Serum from the individual would be checked for the presence of antibodies to the papillomavirus by looking for reaction with the recombinant protein. A significant degree of reaction between the recombinant protein and the serum would indicate that the serum contained an elevated level of antibodies to the papillomavirus, indicating exposure of the patient to that virus.

Proofs of the parties

In their proofs for conception and actual reduction to practice, the parties have attempted to show why their laboratory work at various stages provided sufficient evidence that various limitations of the Counts, particularly the existence of conformational epitopes, had been demonstrated. The parties mutually have challenged the sufficiency of proof each has offered for conception and actual reduction to practice of the counts in the various interferences. In briefest outline, the positions of the parties follow.

Frazer discloses, in its Australian, PCT, and involved applications, particles made from the L1 and L2 proteins of an HPV-16 virus. These particles are significantly smaller (average diameter reported to be 35-40 nm) than all known papillomaviruses (diameters reported to be 50-60 nm). These particles are also irregularly shaped, rather than essentially spherical or icosahedral. Frazer presents no credible evidence that indicates that these particles have conformational epitopes of the native HPV-16 virus. Instead, Frazer maintains that such conformational epitopes are inherently present in the particles it produced. Frazer's position has not been accepted, and it has been denied the benefit for priority of its Australian application. (In constrast, the particles from other papillomaviruses disclosed in

Frazer's PCT application and in its involved application are about 50 nm in diameter and regularly shaped. Motions by Frazer's opponents that the disclosures of these particles failed as constructive reductions to practice of the Count were unsuccessful in the preliminary motions phase. Thus, Frazer was accorded the benefit for priority of its PCT application.)

Schlegel discloses L1 protein from HPV-1, together with experimental evidence that it maintains shows that the L1 protein has the conformational epitopes of the L1 protein in the native virion. Schlegel reports, however, that it looked for but did not find evidence indicating the presence of virus-like particles in its L1 protein preparations.

Lowy discloses virus-like particles and experimental evidence that it maintains shows that the virus-like particles it reports have at least one conformational epitope of the native virus and are capable of inducing neutralizing antibodies to the native virus.

Rose discloses virus-like particles and experimental evidence that it maintains shows that the virus-like particles it reports are conformationally correct and are recognized by antibodies from patients, including human patients, infected by the corresponding virus.

More detailed summaries of the technology and of particular technical issues involved in individual interferences may be found in the various decisions on preliminary motions and decisions on priority dates. We emphasize again that this summary is not a substitute for formal findings of fact in the decisions on priority dates.

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